






Disease characteristics in patients with juvenile- and adult-onset systemic lupus erythematosus: A multi-center comparative study

Sherif M Gamal¹, Nermeen Fouad², Nora Yosry¹, Wael Badr³, Nesreen Sobhy¹

¹Rheumatology, Faculty of Medicine, Cairo University, Cairo, Egypt

²Rheumatology, Faculty of Medicine, Fayoum University, Fayoum, Egypt

³Department of Pediatric, Faculty of Medicine, Fayoum University, Fayoum, Egypt

ABSTRACT

Objectives: This study aims to compare disease characteristics in patients with juvenile-onset systemic lupus erythematosus (JSLE) and adult-onset systemic lupus erythematosus (ASLE).

Patients and methods: Between June 2010 and March 2020, a total of 186 patients with JSLE (23 males, 163 females; median age: 25 years; range, 20 to 30.3 years) and 236 patients with ASLE (23 males, 213 females; median age: 35 years; range, 29 to 40 years) were retrospectively analyzed. Clinical and laboratory data, treatment received, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) scores, comorbidities and deaths were compared between the groups.

Results: The JSLE patients showed statistically significant higher constitutional manifestations, cardiac manifestations, serositis, nephritis, end-stage renal disease, neurological manifestations, gastrointestinal manifestations, secondary vasculitis, Raynaud's, livedo-reticularis, dry mouth, dry eye, ocular manifestations, avascular necrosis, hematological manifestations, and hypocomplementemia ($p < 0.001$, $p = 0.016$, $p = 0.005$, $p = 0.001$, $p = 0.04$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.002$, $p = 0.043$, $p = 0.004$, $p = 0.03$, $p < 0.001$, $p = 0.01$, $p < 0.001$, and $p = 0.001$, respectively). Median SLEDAI scores were statistically significant higher in the JSLE group, both at onset ($p < 0.001$) and in the final follow-up visit ($p < 0.001$). Median SLICC scores were also higher in the JSLE group ($p < 0.001$). Mycophenolate mofetil and intravenous pulse steroids were more frequently used in the juvenile group ($p < 0.001$ and $p = 0.03$, respectively). Hypertension, dyslipidemia, and avascular necrosis were found to be statistically significantly higher in the JSLE group ($p < 0.001$, $p = 0.006$, and $p = 0.01$, respectively). The mortality rate was statistically significantly higher in the JSLE group than the ASLE group ($p < 0.001$).

Conclusion: The JSLE patients showed more serious manifestations, higher disease activity, higher damage index, and mortality rate compared to ASLE patients. These results suggest the need of a regular follow-up and close surveillance of JSLE patients.

Keywords: Adult-onset, juvenile-onset, surveillance, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a multifactorial, multisystem autoimmune disease with extremely varied clinical presentations and fluctuating disease course, ranging from mild with gradual onset to rapidly fulminant multi-organ failure.^{1,2}

Juvenile-onset SLE (JSLE) is one of the most common childhood autoimmune

diseases; approximately 20% of SLE cases are diagnosed in childhood and adolescence, usually at approximately 11 to 12 years of age.^{3,4} It demarcates a subset of individuals that fulfill the classification criteria for SLE in children younger than 16 years.⁵⁻⁷

Previous studies have proposed that the age of disease onset may affect disease expression,

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Correspondence: Nesreen Sobhy, MD. Rheumatology, Faculty of Medicine, Cairo University, 11562 Cairo, Egypt.
Tel: 01002982012 e-mail: nesreen_sobhy@yahoo.com

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serological findings, and the pattern of organ involvement.^{8,9} In general, JSLE is acute, with higher disease activity and severity, and with more permanent damage compared to adult-onset SLE (ASLE).⁸

In most studies comparing JSLE and ASLE, nephritis has been reported to be more common in JSLE patients,¹⁰⁻¹² and mucocutaneous manifestations, neuropsychiatric manifestations, and cytopenia are more frequently reported in JSLE.^{11,12} Torrente-Segarra et al.¹² found that JSLE showed significantly more pleuritis, pericarditis, Raynaud's phenomenon, hypocomplementemia, anti-double-stranded deoxyribonucleic acid (dsDNA), while anti-Ro antibodies, secondary Sjögren syndrome, osteoporosis and fibromyalgia were more common in ASLE. Furthermore, Smith et al.¹³ reported that cutaneous vasculitis was more prevalent in JSLE compared to adult-onset disease.

Although survival rates for patients with JSLE have significantly improved in recent years, morbidity is still high, and most adolescents and young adults with JSLE continue to have an active disease. These patients are still developing new organ involvement and damage,^{14,15} with subsequent impaired health-related quality of life.¹⁶

It is well known that ethnicity and sociodemographic factors affect the characteristics of JSLE.¹⁷ Although JSLE is not uncommon,¹⁸ only a limited number of studies discuss the long-term outcomes of JSLE. In the present study, we aimed to investigate the clinical characteristics, disease activity, and damage among patients with JSLE and compare these clinical characteristics with ASLE patients. Such a characterization may help to raise awareness about this disease category, allowing better understanding of the disease pattern, outcomes and prognosis.

PATIENTS AND METHODS

This multi-center, retrospective, comparative study was conducted at Rheumatology Department in Cairo and Fayoum University, and in Pediatric Department in Fayoum University between June 2010 and March

2020. Medical records of a total of 186 patients with JSLE (23 males, 163 females; median age: 25 years; range, 20 to 30.3 years) and 236 patients with ASLE (23 males, 213 females; median age: 35 years; range, 29 to 40 years) were included. The ASLE patients consisted the control group and were randomly selected. All patients and controls fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for SLE.⁷

The medical records of all patients were reviewed for their demographic, clinical, laboratory, and immunological data, as well as treatment received, complications, associated comorbidities, outcomes, and deaths. Disease activity both at onset and during the last visit according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).¹⁹ and Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) were reported.²⁰

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in median (min-max) or number and frequency. The Kolmogorov-Smirnov test was used for normality testing. Comparisons between the study groups were done using the Mann-Whitney test for quantitative variables and the chi-square test for the qualitative variables. Odds ratios (ORs) were calculated with 95% confidence interval (CI). A two-tailed *p* value of <0.05 was considered statistically significant.

RESULTS

Of a total of 422 patients with SLE, 186 (44.1%) of them were classified as JSLE (age at onset ≤16 years) and 236 were classified as ASLE (age at onset >16 years). The median age of onset was 14 (range, 12 to 15) years and the median disease duration was 12 (range, 6.75 to 17.25) years in the JSLE group. The median age of onset was 25 (range, 21 to 32.75) years and the median disease duration was six (range, 3.25 to 11) years in the ASLE group. There was no significant difference in the sex distribution between the JSLE and ASLE groups (*p*=0.4).

Patients with JSLE showed significantly higher constitutional manifestations, cardiac manifestations, serositis, nephritis, end-stage renal disease, neurological manifestations, gastrointestinal (GI) manifestations, secondary vasculitis, Raynaud's phenomenon, livedo-reticularis, intra-alveolar hemorrhage, secondary sicca (dry mouth and dry eyes), and ocular manifestations compared to the ASLE group. Clinical manifestations are illustrated in Table 1.

Disease activity scores as measured by the SLEDAI were significantly higher in the juvenile group than in the adult group, both at baseline (11 [6 to 17.25] *vs.* 8 [4 to 13], respectively; $p < 0.001$) and at the final visit (4 [0 to 8] *vs.* 0 [0 to 4], respectively; $p < 0.001$). Similarly, SDIs measured by the SLICC scores were also higher in the juvenile group (1 [0 to 2] *vs.* 0 [0 to 1], respectively; $p < 0.001$).

Hematological manifestations ($p < 0.001$) and hypocomplementemia ($p = 0.001$) were significantly more frequent in the JSLE group. Laboratory test results are shown in Table 2.

The median steroid dose given during the last visit was 15 (range, 9.3 to 25) mg in patients with JSLE and 10 (range, 5 to 20) mg in patients with ASLE.

Mycophenolate mofetil (MMF) ($p < 0.001$) and intravenous (IV) pulse steroids ($p = 0.034$) were more frequently used in JSLE. Otherwise, no significant differences were found in the other treatment options (Table 3).

Hypertension, dyslipidemia and avascular necrosis were found to be significantly higher in the patients with JSLE than ASLE ($p < 0.001$, $p = 0.006$, and $p = 0.01$, respectively) (Table 4).

In addition, JSLE patients showed a statistically significant higher mortality rate compared to ASLE patients (34/186, 18.3% *vs.* 13/236, 5.5%, respectively; $p < 0.001$), with infection in 6/34 (17.6%) and single organ failure (e.g., renal failure) in 6/34 (17.6%) being the most reported causes of deaths in the JSLE patients. Other causes of death included alveolar hemorrhage in 3/34 (8.8%), bleeding peptic ulcer in 1/34 (2.9%), and

Table 1. Clinical manifestations of the participants

	Juvenile-onset lupus (n=186)		Adult-onset lupus (n=236)		p
	n	%	n	%	
Constitutional manifestations	153	82.3	158	66.9	<0.001
Mucocutaneous manifestations	164	88.2	194	82.2	0.09
Pulmonary manifestations	107	57.5	117	49.6	0.104
Cardiac manifestations	54	29.0	45	19.1	0.016
Serositis	106	57.0	102	43.2	0.005
Nephritis	140	75.3	143	60.6	0.001
End stage renal disease	17	9.1	10	4.2	0.04
Neurological manifestations	87	46.8	70	29.7	<0.001
Gastrointestinal manifestations	48	25.8	23	9.7	<0.001
Musculoskeletal manifestations	164	88.2	209	88.6	0.902
Secondary vasculitis	71	38.1	54	22.8	<0.001
Thrombosis	22	11.8	43	18.2	0.07
Raynaud's phenomenon	51	27.4	36	15.3	0.002
Livedo-reticularis	11	5.9	5	2.1	0.043
Digital gangrene	7	3.8	5	2.1	0.3
Intra-alveolar hemorrhage	5	2.7	1	0.4	0.092
Dry mouth	15	8.1	5	2.1	0.004
Dry eye	11	5.9	4	1.7	0.03
Ocular manifestations	27	14.5	10	4.2	<0.001
Pulmonary hypertension	24	12.9	20	8.5	0.14

Table 2. Laboratory data of the participants

	Juvenile-onset lupus (n=186)		Adult-onset lupus (n=236)		p
	n	%	n	%	
Hematological manifestations	176	94.6	190	80.5	<0.001
Anemia throughout the disease	168	90.3	187	79.2	0.002
Leukopenia throughout	96	51.6	93	39.4	0.012
Thrombocytopenia throughout	79	42.5	46	19.5	<0.001
ANA positivity	177/182	97.3	228/235	97	0.89
Anti-dsDNA antibodies positivity	116/154	75.3	156/229	68.1	0.1
Hypocomplementemia	63/158	39.9	54/223	24.2	0.001
APL antibody positivity	58/131	44.3	65/183	35.5	0.1

ANA: Antinuclear antibody; Anti-dsDNA: Anti-double-stranded deoxyribonucleic acid; APL: Anti-phospholipid.

Table 3. Treatment options given to participants

	Juvenile-onset lupus (n=186)		Adult-onset lupus (n=236)		p
	n	%	n	%	
Cyclophosphamide	105	56.5	115	48.7	0.11
Azathioprine	147	79.0	168	71.2	0.066
Antimalarial	176	94.6	223	94.5	0.95
MMF	77	41.4	45	19.1	<0.001
IV pulse steroids	147	79.0	165	69.9	0.034

MMF: Mycophenolate mofetil; IV: Intravenous.

Table 4. Associated comorbidities of participants

	Juvenile-onset lupus (n=186)		Adult-onset lupus (n=236)		p
	n	%	n	%	
Hypertension	82	44.1	64	27.1	<0.001
Diabetes mellitus	12	6.5	19	8.1	0.5
Dyslipidemia	75	40.3	65	27.5	0.006
Thyroid dysfunction	10	5.4	7	3.0	0.21
Malignancy	1	0.5	0	0	0.44
Osteoporosis	27/150	18	34	14.4	0.3
Avascular necrosis	23	12.4	13	5.5	0.01

pulmonary edema in 1/34 (2.9%). Combination of (single organ failure and infection), (alveolar hemorrhage and infection), and (organ failure with infection and alveolar hemorrhage) were recorded as the cause of death in 3/34 (8.8%). In 14/34 (41.2%) of the JSLE patients, the exact cause of death could not be identified

due to either home death or missing data in the medical records.

DISCUSSION

In this study, we assessed the clinical, immunological, and serological characteristics

of 186 patients with JSLE and compared these findings with those of 236 patients with ASLE. Although many studies have addressed the clinical and immunological features of JSLE, only a few comparisons between JSLE and ASLE have been made, and most of which have conflicting results.

Our study showed that the female-to-male ratio was 7:1 and 9:1 in JSLE and ASLE, respectively. The sex ratio of ASLE was similar to previous studies,^{21,22} while that of JSLE was lower than the previous reports.²³ In a study by Gheita et al.,²⁴ the female-to-male ratio was 6.7:1 and 10.5:1 for JSLE and ASLE, respectively, consistent with our findings. However, a lower female-to-male ratio in JSLE was reported in other studies from Saudi Arabia²⁵ and Kuwait.²⁶

While comparing the prevalence of clinical manifestations between JSLE and ASLE, we found that JSLE showed significantly higher rates of constitutional, cardiac, neurological and GI manifestations. These patients were also more likely to develop serositis, nephritis, end-stage renal disease, and secondary vasculitis compared to their adult counterparts. Mucocutaneous and musculoskeletal manifestations are the most common clinical manifestations in JSLE, whereas musculoskeletal manifestations are the most common clinical manifestations in ASLE. Our findings are similar to previous reports.²⁵⁻²⁸

There are variations between the studies regarding the prevalence of various clinical manifestations. In a study, there was no significant difference between ASLE and JSLE regarding serositis and constitutional, mucocutaneous, renal, and vascular manifestations.²⁹ Another study from Egypt showed that nephritis and neuropsychiatric and hematological manifestations occurred more frequently in children.²⁷ Similar findings were also described previously.³⁰⁻³² In a large-scale Turkish study, nephritis, neurological, mucocutaneous and hematological manifestations were more frequent in JSLE patients.¹¹ Similar findings were reported in das Chagas Medeiros et al.'s,¹⁰ Torrente-Segarra et al.'s,¹² and Brunner et al.'s¹⁶ studies. This variability is mostly due to different sample sizes and selection criteria including different age groups among JSLE. Other causes may be race, ethnicity, and environmental and developmental factors.

In the present study, the SLEDAI scores were significantly higher in patients with JSLE than in patients with ASLE. This finding is consistent with previous studies.^{27,29,33,34} Systemic lupus erythematosus-related major organ involvement such as nephritis and neuropsychiatric manifestations may be the main cause of the increased SLEDAI scores.²⁷ Moreover, adults seem to respond better to treatment and are able to achieve and maintain remission in a shorter period compared to juveniles.³⁰ It may also highlight the possibility that the current medications available for ASLE may not work as efficiently in JSLE.

Similarly, the SLICC damage scores were also higher in the patients with JSLE in our study, consistent with a previous study.²⁴ The increased scores in JSLE were mainly attributed to renal and musculoskeletal damage. Moreover, regardless of the damage index used, damage in JSLE is always higher than that in ASLE. In a study by Brunner et al.,³⁰ the SLICC/ACR SDI was used as to measure disease damage. Although SDI is more directly related to aging (by assessing cataracts, myocardial infarction, and diabetes mellitus), patients with JSLE still had a higher disease damage index than patients with ASLE in our study. This can be explained by the increased disease activity and higher levels of corticosteroids and immunosuppressive agents required for disease control in children, compared to adults.³⁰

Serological analysis showed that complement consumption was significantly more frequent in JSLE, whereas antinuclear antibody (ANA), anti-dsDNA, and anti-phospholipid (APL) antibodies showed no significant difference. A review of the current literature reveals some variations in serological abnormalities; complement consumption is a common finding in many studies.^{27,35} Other studies have shown that serum C3 is consumed without significant differences between the groups, whereas serum C4 was lower than normal in JSLE, but not in ASLE.^{3,29} The C3 is correlated with nephritis activity and, as patients with JSLE are more likely to develop active and progressive nephritis than patients with ASLE, C3 consumption levels are usually higher in this group.²⁷ Similar to our results, previous studies found no significant differences between the levels of ANA and

anti-dsDNA antibodies in both groups.^{3,10,36} On the other hand, some studies found that anti-dsDNA antibodies were more frequently detected in children.^{27,37} Regarding the APL antibodies, we had similar results with a previous study by Gyo et al.³⁶ However, some other studies found higher APL antibodies in patients with JSLE.^{27,38}

In the current study, MMF and IV pulse steroids were more frequently used in JSLE than in ASLE. Comparative studies between adults and children found that JSLE was more frequently treated with high doses of corticosteroids and immunosuppressive medications than ASLE.³⁹ In a study by Brunner et al.,³⁰ children with SLE were treated with IV methylprednisolone almost three times more often than adults with SLE. This may be explained by the more active, poorly controlled disease in JSLE compared to ASLE.

In our study, hypertension, dyslipidemia, and avascular necrosis were significantly higher in JSLE than in ASLE. The association of these comorbidities with JSLE can be explained by the higher prevalence of nephritis in JSLE and, consequently, the higher need of IV pulse and oral steroid.

The association between corticosteroids and avascular necrosis has been shown in previous studies.^{40,41} Furthermore, hypertension and dyslipidemia are considered risk factors for avascular necrosis,^{40,41} which may explain the higher incidence of avascular necrosis among our JSLE patients.

In our study, JSLE was found to have significantly higher mortality rates compared to ASLE (18.3% vs. 5.5%, respectively; $p < 0.001$). Although most reports have shown a decline in mortality rates among JSLE, this is still higher than the general population. Mortality in JSLE is five times higher than in ASLE patients. The main causes of death in our pediatric patients were infection and organ failure, consistent with the literature.^{26,42,43} Since JSLE is associated with higher disease activity, damage indices, and comorbidities, it is unsurprising that JSLE has higher mortality rates with diverse causes of mortality.

The main strength of this study is the large number of patients with JSLE, recruited from two different centers. On the other hand, due to

the retrospective nature of the study, potential limitations include the inability to retrieve some missing data as cumulative oral steroid dose for each patient, detailed causes of mortality in some patients, and anti-Ro antibody results.

In conclusion, our study findings provide a better understanding of the clinical characteristics, disease activity, long-term outcomes, and damage in JSLE patients. These results highlight the importance of close monitoring, follow-up, and adequate management of JSLE to minimize the increased morbidity and mortality of these young patients in the future.

Ethics Committee Approval: The study was approved by the participating department in Cairo and Fayoum University in January 2019. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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